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Current Pharmaceutical Design, **2017**, *23*, **1-6** **1**

REVIEW ARTICLE

Biosimilars: From Extrapolation into Off Label Use

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ARTICLE HISTORY

Received: October 29, 2017
Accepted: November 24, 2017

DOI:
10.2174/1381612824666171129193258

Abstract: ***Background*:** Biologic drugs have revolutionised the management of many inflammatory conditions. Patent expirations have stimulated development of highly similar but non-identical molecules, the biosimilars. Extrapolation of indications is a key concept in the development of biosimilars. However, this has been met with concerns around mechanisms of action, equivalence in efficacy and immunogenicity, which are reviewed in this article.

***Methods*:** Narrative overview composed from literature search and the authors' experience. Literature search included Pubmed, Web of Science, and online document archives of the Food and Drug Administration and European Medicines Agency.

***Results*:** The concepts of biosimilarity and extrapolation of indications are revisited. Concerns around extrapolation are exemplified using the biosimilar infliximab, CT-P13, focusing on mechanisms of action, immunogenicity and trial design. The opportunities and cautions for using biologics and biosimilars in unlicensed inflammatory conditions are reviewed.

***Conclusions*:** Biosimilars offer many potential opportunities in improving treatment access and increasing treatment options. The high cost associated with marketing approval means that many bio-originators may never become licenced for rarer inflammatory conditions, despite clinical efficacy. Biosimilars, with lower acquisition cost, may improve access for off-label use of biologics in the management of these patients. They may also provide opportunities to explore off-label treatment of conditions where biologic therapy is less established. However, this potential advantage must be balanced with the awareness that off-label prescribing can potentially expose patients to risky and ineffective treatments. Post-marketing surveillance is critical to developing long-term evidence to provide assurances on efficacy as well as safety.

Keywords: Biosimilar, extrapolation, off-label, monoclonal antibody, anti-TNF, rheumatoid arthritis, ankylosing spondylitis.

1. INTRODUCTION

Biologic drugs have revolutionised the management of many immune-mediated inflammatory conditions ranging from rheumatoid arthritis (RA) to inflammatory bowel disease (IBD). These drugs are extremely effective, yet also carry high acquisition costs. In the case of rheumatic diseases, they heralded the development of a market for high cost drugs, previously considered impossible and, in parallel, identified inflammatory diseases as attractive conditions for Industry to invest in [1]. The limited lifespan of patents for these drugs has stimulated programmes, many starting over a decade ago, to develop similar molecules that, whilst not identical to the originator, could be considered to be biological equivalent of a "generic". Such "biosimilars" are defined as a biological agents that are similar in terms of quality, safety and efficacy to an already licensed reference product [2]. To help drive down cost, regulators such as the European Medicines Agency (EMA) and the US Food and Drugs Administration (FDA) have allowed biosimilars to follow an expedited process for approval. Such a process can vastly reduce development costs, which can be passed on to healthcare systems as lower drug cost. Though as a compromise, they are not as extensively investigated as the reference product not only in gaining their licence (of crucial interest to biosimilar companies) but also in post-marketing evaluation for new indications (typically considered not cost-effective for major investment from Industry). This article reviews extrapolation of biosimilar indications and explores the issues and opportunities presented by biosimilars with a focus on off-label use.

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2. BIOSIMILARITY AND EXTRAPOLATION OF INDICATIONS

The prototype class of anti-inflammatory biologic are the anti-tumour necrosis factors (TNF). Both etanercept (a fusion protein comprising two human p75 monoclonal TNF receptors, coupled to a human IgG1 Fc tail) and the monoclonal anti-TNF antibodies (infliximab, adalimumab, golimumab and the PEGylated certolizumab) are large, mainly protein, molecules. They are produced by recombinant DNA techniques using a single clone of cells through a highly refined process. In the manufacturing process, primary amino-acid sequences undergo post-translational modifications such as sialyation, that are affected by the cell line and their environment [3]. This creates specific protein-folding and complex three dimensional structures. Each manufacturer uses a unique cell line and production process, therefore copies cannot be identical to the reference product (RP) [4]. In fact, no two batches of any biologic, even the RP, can be identical [5].

For each marketed indication, approval for the RP relies on clinical trials to demonstrate efficacy, safety and immunogenicity. In contrast, biosimilar approval does not require the manufacturer to re-establish efficacy, but is instead based on the demonstration that there are no clinically meaningful differences from the RP. This involves comprehensive comparison firstly of structure and function through complex analytical and in vitro studies, then in vivo animal studies and, finally, abridged clinical studies of pharmacokinetics, pharmacodynamics, immunogenicity, safety and efficacy [2, 6, 7].

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Table 1. Approval status of proposed biosimilars of infliximab, etanercept, adalimumab, and rituximab, as of November 2017.

	Biosimilar	EMA approval status	FDA approval status
Infliximab	**CT-P13**	**Remsima/Inflectra** **Approved** Sept 2013	**Inflectra** **Approved** Apr 2016
	SB2	**Flixabi** **Approved** May 2016	**Renflexis** **Approved** Apr 2017
	PF-06438179	NS	N/A
	BOW015	NS	NS
	ABP710	NS	NS
Adalimumab	ABP501	**Solymbic** **Approved** Jan 2017	**Amjevita** **Approved** Sept 2016
	BI 695501	Cyltezo Approved Nov 2017	Cyltezo Approved Aug 2017
	SB5	Imraldi Approved Jun 2017	NS
	CHS-1420	NS	NS
	GP2017	NS	NS
	M923	NS	NS
	BCD-057	NS	NS
	PF-06410293	NS	NS
Etanercept	**SB4**	**Benepali** **Approved** Jan 2016	NS
	GP2015	Erelzi Approved Jun 2017	**Erelzi** **Approved** Aug 2016
	CHS-0214	NS	NS
	HD203	NS	NS
	LBEC0101	NS	NS
	ENIA11 (TuNEX)	NS	NS
Rituximab	CT-P10	**Truxima** **Approved** Dec 2016	NS
	GP2013	Rixathon Approved Jun 2017	NS
	ABP798	NS	NS
	PF-05280586	NS	NS
	BCD-020	NS	NS

NS, not submitted; N/A, not applicable.

Once biosimilarity has been established in one indication, the drug may be approved for additional indications held by the RP without comparative clinical trials. Extrapolation of indication is integral to the concept of biosimilarity. It reduces the number and size of clinical trials required, thereby decreasing financial cost and, potentially, increasing access [7]. It is however worth noting that the dramatic cost reductions and improved access for small-molecule generics were due to automatic substitution at the pharmacy level [8]. This is not currently the case for biosimilars in most regions. Full "interchangeability" requires additional standards that are currently lacking, as each biosimilar is compared only to the RP, without any evaluation of potential swapping between two or more biosimilars for the same RP.

The concept of biosimilar extrapolation is not new. Regulation was less complex for biosimilar recombinant human protein analogues, such as epoetin and filgrastim, where each mechanism of action is mediated by the same receptor [9]. In contrast, mAbs are much more complex molecules; comprising Fab and Fc regions, each with considerable diversity and variable mechanisms of action. The Fab region can neutralise soluble TNF (sTNF) and remove them from the immune pathway. They can also bind to transmembrane TNF (tmTNF) and activate intracellular signalling resulting in apoptosis or cytokine suppression [10, 11]. The Fc region has the ability to bind to specific receptors, leading to potential effector functions such as antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity, and antibody-dependent cellular phagocytosis. Binding to the neonatal Fc receptor (FcRn) also protects the mAb from proteolytic degradation [12].

3. CONCERNS AROUND EXTRAPOLATION

The biosimilar infliximab CT-P13 was the first to be licensed in the US and EU (see Table **1** for other biosimilars). Comprehensive comparative analyses were supported by two clinical trials demonstrating that pharmacokinetics (PK), efficacy, safety and immunogenicity were comparable in ankylosing spondylitis (AS) and RA [13-16]. Extension studies also demonstrated unaffected safety, efficacy and immunogenicity when switched from the RP [17, 18]. In the US and EU, CT-P13 indication was then extrapolated to all RP indications for psoriasis, psoriatic arthritis, Crohn's disease and ulcerative colitis [19, 20]. This was however met with much controversy for several reasons.

Although TNF may play a pivotal role in the immune pathway of all six disease indications, it is clear that various mechanisms of action are not of equal importance in each condition. Reverse signalling via tmTNF binding is thought to be an important mechanism of action in IBD [11]. This is supported by the fact that etanercept, which binds less avidly to tmTNF, is effective in rheumatic indications but not in IBD [21]. Another mechanism of action thought to be relevant in IBD is natural killer (NK) cell induced target cell lysis, although this had been contested [22, 23]. Compared to its RP, CT-P13 had reduced binding to NK cell FcγRIIIa (low affinity immunoglobulin γ Fc region receptor IIIa) and for this reason was not approved for IBD in Canada [24].

Concern around immunogenicity is another suggested reason to limit extrapolation, as anti-drug antibodies (ADAs) can affect safety and efficacy [25]. For example, a minor change in the manufacturing process of epoetin was thought to have caused autoantibodies to endogenous erythropoietin and the dramatically increased incidence of pure red cell aplasia - a rare but potentially fatal condition [26]. Similarly, infliximab ADA positive Crohn's patients were much more likely to experience infusion reactions [27].

Comparing immunogenicity is difficult, for example ADA was reported in up to 61% in Crohn's disease [27], but varied significantly depending on concomitant medication [28]. However, there do seem to be situations where the frequency of ADAs differs from one disease to another, possibly due to the immunological background underlying the inflammatory process. For example, around 48% of RA patients developed ADAs to infliximab at 30 weeks, compared with 23-27% of AS patients [13, 15].

Lastly, there were concerns around having RA as the disease model to demonstrate comparability between CT-P13 and the RP. Unlike biomarker endpoints used in biosimilar studies of recombinant human protein analogues, mAb trials rely on less sensitive clinical outcomes due to their complex mechanisms of action. A large treatment-placebo effect difference is therefore necessary to reliably demonstrate equivalence. Of the six infliximab indications, RA was associated with one of the smallest placebo-adjusted response [29, 30]. It may therefore not be the most sensitive clinical model to detect a potential difference in efficacy between CT-P13 and its RP. Similarly for immunogenicity, the population with the highest immune response should be used to provide the best sensitivity in detecting differences [31]. RA studies reported less infliximab ADA development [30, 32] compared with Crohn's disease [27] or psoriasis [33]. In summary, the RA studies of efficacy and immunogenicity equivalence did not exclude the possibility that CT-P13 and its RP are different in extrapolated indications, where differences may be more easily detected. Experts therefore argued that dedicated clinical trials were needed for each indication and many clinicians hesitated to use biosimilars even when regulatory approval for extrapolation was granted [34-36]. It was only with subsequent real world data and confirmatory studies that practice began to change [37, 38]. This highlights the need to have additional post-market monitoring to develop long-term evidence to provide assurances on efficacy as well as safety.

4. OPPORTUNITIES FROM BIOSIMILARS

Controversies aside, the dawn of biosimilar mAbs presents many potential opportunities as a result of their reduced cost [39]. The most obvious is the hope to increase drug access or to reinvest savings for other health resources. Take for example biosimilar filgrastim (a granulocyte colony-stimulating factor) which was launched in late 2008. With their reduced cost, funding agencies in the UK updated guidelines which saw use of both RP and biosimilar filgrastim increase by over 100% in the subsequent six years [40]. A significant number of these patients may not have otherwise received the drug.

In 2008, the then named National Institute for Clinical Excellence (NICE) rejected RP infliximab for AS on the grounds of cost-effectiveness [41]. The cost of biosimilar infliximab and its impact on the RP cost, meant that in 2016 NICE reissued guidance that recommended infliximab if the patient is started on the least expensive product [42]. This increased access to TNF inhibition therapy, and also increased the number of treatment options for these patients.

For IBD, the UK Royal College of Physicians' annual audit of biologics suggested that the introduction of biosimilar infliximab could half the annual cost of treatment [43]. This would save the health services an estimated £90 million per year if all patients were switched to a biosimilar [44]. The 2016 audit, which captured the introduction of biosimilar infliximab in 2015, reported the largest annual increase in the absolute number of biologic-treated patients; 22% of patients were prescribed biosimilar infliximab [45]. In addition to licenced indications, biosimilars may also improve access to biologics for other unlicensed inflammatory conditions.

5. OFF-LABEL USE OF BIOSIMILARS

Many of the issues of biosimilars discussed so far have focused on considerations of regulatory agencies. However, these agencies do not have authority over the use of drugs outside of their licensed indications. Health care professionals can prescribe drugs "off-label" to treat (typically rare) conditions other than those formally approved. There are several reasons why off-label prescribing exists [46]. The most pertinent, in the case of biologics, is related to their cost.

For any biologic, obtaining approval for a new indication requires extensive and costly clinical studies. In the US, licence approval requires two randomised, placebo-controlled clinical trials that demonstrate both efficacy and safety in the disease for which the indication is being sought [47]. If a disease is uncommon, such trials will be difficult to conduct and, even if approved, the revenue may not offset costs in obtaining approval. Consequently, there are many inflammatory diseases which share common pathological pathways but may never receive licence as an indication. Of course, biosimilar development and usage may be very different in Asia and the third world countries, where regulatory requirements for biosimilar approval vary and are less stringent.

There are many instances where biologics have been successful in treating unlicensed inflammatory diseases [48]. Indeed some off-label uses are integral to disease management and recommended in guidelines. For example infliximab for Behçet's disease [49] or rituximab in refractory lupus, lupus nephritis [50, 51] and ANCA associated vasculitis (AAV) [52, 53]. Greater accessibility to biologics may improve management of patients with such unlicensed indications. For example in AAV, rituximab is non-inferior to cyclophosphamide for remission induction [54, 55] with preferable qualities with respect to fertility and infection concerns. However, the cost-effectiveness of rituximab had been raised as a concern [56]. The emergence of rituximab biosimilars will undoubtedly improve care for patients with AAV or other conditions where rituximab is as effective as cyclophosphamide.

Reduced biologic costs may also promote further controlled trials to generate higher quality evidence, such as for inflammatory myositis [57]. Additionally, more opportunities may open up to explore off-label treatment of conditions where biologic therapy is less established, such as TNF inhibition for polymyalgia rheumatica [58] or giant cell arteritis [59, 60]. However, it is worth noting that biosimilar manufacturers will be unlikely to seek approval for additional indications. Once licensed, a biosimilar needs to go through the same approval process as the RP for additional indications. If the RP were to obtain new indications, extrapolation of indications in the biosimilar no longer applies.

There is concern that if a drug can be used off-label, patients have less incentive to enrol in trials where they may receive a placebo. This may reduce opportunity to develop rigorous data and could explain why most off-label studies are anecdotal reports [48]. Most importantly, unregulated off-label prescribing can potentially expose patients to risky and ineffective treatments [61]. Therefore off-label use must be applied with the same level of caution as for the RP [62]. Post-market monitoring is essential to develop long-term evidence and provide assurances on efficacy as well as safety.

6. PHARMACOVIGILANCE

Given the nature of biologics and their production, the model used for drug safety monitoring of small-molecule generics is inadequate. Pharmacovigilance systems need to be able to distinguish between adverse events associated with the biosimilar from those of its RP. Therefore, the UK's Medicines and Healthcare products Regulatory Agency (MHRA) recommends that all biologics, including biosimilars, are prescribed by brand name rather than International Non-proprietary Name [63, 64].

As with all new medicines, biosimilars have a 'black triangle' for usually two years post-approval to encourage reporting of suspected adverse drug reactions (ADR). The MHRA's Yellow Card scheme in the UK requires such reports to provide the brand name and batch number to aid traceability [65]. This information should also be provided to patients to help more accurate reporting. In the US, similar post-approval safety surveillance is performed using voluntary reporting systems. There is also a system of active surveillance using retrospective analysis of medical records and drug event monitoring using patient surveys [66].

The EMA also recommends that all biosimilar manufactures should participate in existing pharmacoepidemiological studies, such as registries that have been set up primarily to monitor safety [67]. The British Society for Rheumatology (BSR) recommends that all patients using biosimilars should be registered with the BSR biologics register [68].

CONCLUSION

The emergence of biosimilars heralds an exciting time for the management of inflammatory diseases. Extrapolation of indication is integral to the concept of biosimilar development. The consequent cost reductions will improve access, increase treatment options, and help resource reallocation to research in hitherto low volume but high-impact diseases. The use of biosimilars should, however, be approached with similar levels of caution as with their RP and robust mechanisms should be in place for efficacy assessments and pharmacovigilance.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

RJM has received research grant funding, acted as a scientific advisor to or spoken at meetings sponsored by: Abbvie, AKL, Biogen, BMS, Chugai, Genzyme, Hospira, MSD, Novartis, Pfizer, Regeneron, Roche, Sandoz, Sanofi, UCB Pharma.

ACKNOWLEDGEMENTS

Declared none.

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